Fifth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease

Soy Protein Allergy: Incidence and Relative Severity[1,2]

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ABSTRACT Food allergy is a relatively rare and sometimes violent reaction of the immune system to food proteins. The first report characterizing soy allergy appeared in 1934. The Food and Agriculture Organization of the United Nations includes soy in its list of the 8 most significant food allergens. At least 16 potential soy protein allergens have been identified but their relative clinical significance is unknown. Conversely, soy has a long history of successful use in managing cow's milk allergies in infants. To better predict the utility of soy proteins for controlling food allergy, it is important to understand the relative allergenic reactivity of soy compared with other major food proteins. This can be studied using clinical data, animal models, and biochemical approaches; all show diminished reactivity for soy. Clinical studies using in vitro methods and blinded food challenges have generated substantial information. Study populations include high-risk asymptomatic infants and patients with atopic symptoms, positive food challenges, and specific milk allergies. Generally, these studies show lower allergic reactivity for soy proteins vs. other food allergens. Comparisons of food allergen dose-response relationships for triggering allergic symptoms also demonstrate a higher protein concentration threshold for soy (~100 times), indicating lower allergenic reactivity. Extensive investigations of soy immunological reactivity have also been carried out using animal models. Consistent with clinical results, all of these data show substantially diminished immunological reactivity for soy proteins. Biochemical and immunochemical analyses indicate no striking differences between soy and other food proteins that would explain these unexpected differences in allergenic reactivity. J. Nutr. 134: 1213S–1219S, 2004.

KEY WORDS: • *soy* • *food allergy* • *clinical results* • *animal models*

Food allergy (FA)[4] is a relatively rare and sometimes violent immune system reaction to food proteins. In its broadest definition FA includes syndromes involving several immune mechanisms, each causing a variety of symptoms. Although all types of FA must be effectively managed, the most dangerous is immediate-type hypersensitivity (type I) mediated by IgE antibodies to food proteins. Most type I FA appears in the first 2 y of life and occurs in 6–8% of infants (1). As their immune systems mature (by 5 y), ~80% of allergic infants will lose their FAs (2). Symptoms range from mild rashes to life-threatening systemic anaphylaxis and are of 4 main types: dermatological (hives, local swelling, dermatitis, and eczema), gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), respiratory (runny nose, asthma, and tightening of the throat), and systemic (anaphylactic shock, organ failure, cardiac arrhythmia, and death).

Foods vary in clinical allergy significance. Although all food proteins have the potential to be allergenic for some people, 8 foods have been identified as the most frequent human food allergens and account for ~90% of FAs. These foods are milk, eggs, fish, crustacea, wheat, peanuts, tree nuts, and soy (3). This article describes the allergenic potential of soy proteins compared with some of the other major food allergens.

Immunology of food allergy

A detailed description of the mechanisms of food allergy is beyond the scope of this article, but several excellent reviews of clinical aspects are available (4–6). Briefly, type I food allergies involve a 3-step process. The first step is sensitization, which begins with transit of relatively intact food antigens across the intestinal barrier. The gut may be unable to effectively exclude intact antigens because of immaturity, injury, or infection. Some intact food antigen uptake is normal, even in adults. Factors affecting whether the antigens stimulate the usual antibody responses (IgG and IgA) and immune tolerance

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[4] Abbreviations used: CMF, cow milk protein–based formula; DBPCFC, double-blinded, placebo-controlled, food challenge; FA, food allergy; RAST, radioallergosorbent test; SF, soy protein-based formula; SPT, skin prick test.

or an allergic response are not clearly understood. In individuals predisposed to allergy, food antigens generate activated antigen-specific B cells and a special set of helper T cells that direct B cells to differentiate into IgE-producing plasma cells. Once secreted, IgE is quickly bound by high-affinity IgE receptors mainly on the surface of mast cells. These cells contain large amounts of histamine and other allergic reaction mediators and are the main inducers of symptoms of allergy. The end result of sensitization is the presence in circulation and tissues of large numbers of mast cells armed by allergen-specific IgE antibodies on the cell surface.

In the second step, triggering, which occurs some time after sensitization, allergen or multivalent allergen fragments are again absorbed after ingestion. IgE antibodies on mast cells bind the allergen so that the allergen cross-links at least 2 receptor-bound IgE molecules. This creates a signal causing the mast cell to release histamine and other inflammatory mediators (degranulation). Timing and magnitude of the release is defined by allergen dose and a number of poorly understood host factors.

The final step, the initiation of clinical symptoms, occurs when histamine and other inflammatory mediators stimulate the wide variety of allergic symptoms in other cells and organs. With this basic understanding of the allergy process we can now consider soy allergy.

Soy allergy characterization

Soy protein is allergenic. The first allergic reactions to soy in humans were described in 1934 (7). Anti-soy IgE antibodies have been identified but allergen specificity patterns are variable and complex. As many as 28 soy proteins bind to IgE from soy-allergic patients (8). Soy is also an aeroallergen, although the pathologies and allergen reactivity profiles are different for ingestion versus inhalation, where soy hull antigens not present in soy protein isolates seem to dominate (9). A small number of fatal allergic reactions to soy have been reported (10,11), but in all cases victims also had severe peanut allergies and asthma.

What is the relative allergenic reactivity of soy proteins compared with other major food proteins? The answer depends on what clinical and laboratory outcomes are used and which patient populations are studied.

Clinical and laboratory indicators of allergy. Clinical indicators of food allergy include cumulative clinical history of atopic symptoms; history of allergic symptoms soon after specific food ingestion; positive skin prick test (SPT) with food protein extracts; unblinded food challenges; and double-blinded, placebo-controlled, food challenges (DBPCFCs; the gold standard for food allergy diagnosis). Laboratory indicators of food allergy are radio allergosorbent test (RAST), which measures allergen-specific IgE antibodies using radioisotopes; ELISA, which also measures allergen-specific IgE using antibody-conjugated enzymes and chromatic substrates; and immunoblotting of polyacrylamide gel electrophoresis-separated proteins to reveal IgE-allergen binding.

Patient populations. Allergy assessment outcomes can be influenced by the criteria used to define patient enrollment. A variety of clinical populations have been used to study food allergy. Within specific populations, enrollment standards for inclusion and exclusion also vary. When comparing similar studies, it is important to clearly understand the characteristics used to qualify and enroll study subjects. Five clinical populations have been used for most food allergy research: 1) "high-risk" asymptomatic infants (defined variably based on the atopic history status of parents and/or siblings; 2) patients with atopic symptoms (defined variably to include 1 to several allergy-associated symptoms); 3) patients with positive DBPCFCs (a relatively rigorous criterion); 4) patients with cow's milk allergy (a subset of group 3 that have been rigorously identified using DBPCFCs); and 5) whole-population birth cohorts.

Clinical results

High-risk infants fed cow's milk protein–based formula (CMF) versus soy protein-based formula (SF). Concern exists about the sensitivity of cumulative atopic symptom scores as indicators of food allergy status, especially for older infants. These subjects may no longer be taking formula and have been exposed to a wide variety of nonfood environmental allergens that may contribute to their atopic symptoms. Some studies show no difference in the cumulative history of atopic symptoms (12–15). Other studies report significantly less asthma, less rhinitis, or generally reduced atopy for SF-fed infants (16–18). In the Halpern study (18) where milk allergy in CMF-fed infants was compared with soy allergy in SF-fed infants, food allergy was reduced 3.6 fold with soy. A meta-analysis of allergen reactivity patterns in 17 studies of high-risk infants shows soy allergy occurring in 3–4% of subjects versus 25% for cow's milk (19).

Patients with atopic symptoms. These studies surveyed the clinical reactivity specificities of infants and children with atopic symptoms; the diagnostic tests used were RAST, SPT, or DBPCFC. Four studies demonstrate the overall incidence of reactivity to soy. Giampietro et al. (20) studied 317 atopic children and found 22% positive to soy by RAST but only 3% were positive by DBPCFC. Magnolfi et al. (21) tested 704 atopic children and found 21% soy positive by SPT and only 1.3% soy positive by DBPCFC. Bruno et al. (22) tested 505 atopic children and found 6% soy positive by SPT and 1.2% soy positive by DBPCFC. Burks et al. (23) found 13% soy positive by SPT and 1.8% soy positive by DBPCFC in a study of 165 atopic patients. Overall, these data show a relatively low rate of soy allergy in atopic infants (28 of 1691 patients, 1.7%) and a relatively high rate of false-positive results when SPT and RAST are used to diagnose symptomatic soy food allergy.

Soy reactivity in DBPCFC-positive subjects. Two reports summarized results of DBPCFC patient evaluations performed at major tertiary care allergy centers. Bock and Adkins (24) describe 185 positive food challenges conducted over 16 y, where 31% were positive for cow's milk proteins and 8% (15 patients) were positive for soy. Sicherer et al. (25) reported on 196 positive DBPCFCs completed over 13 y, with 23% positive for cow's milk proteins and 10% (20 patients) positive for soy proteins. With fewer than 35 soy-positive patients identified by DBPCFC over 13 y by 2 of the prominent academic food allergy research groups in the United States, it is apparent that extensive studies of soy-allergic subjects in America would be a daunting task. Patients with soy allergy confirmed by DBPCFC seem very rare.

Soy allergy in patients with cow's milk allergy. Most often, SF is used clinically to manage intolerance to CMF. A variety of mechanisms are involved in CMF intolerance, which currently affects as many as 36% of infants at some point in y 1 of life. Infants with type I milk protein allergy are estimated to be 6–8% of the total population, so most (~80%) CMF intolerance is not caused by allergy and is effectively managed using SF. Infants with type I allergy to

CMF are a rigorous test population for evaluating the allergenic reactivity of SF.

Several studies have measured the proportion of infants with documented CMF allergy that will develop soy allergy when SF is substituted for CMF. Bock and Adkins (24) reported 4 of 54 (7%) CMF-allergic infants developed soy allergy when switched to SF. Cantini et al. (26) found 1 of 20 (5%) who developed soy allergy in a similar study. Zeiger et al. (27) observed 13 of 93 (14%) infants allergic to CMF who developed soy allergy. In the study by Kleinola et al. (28), 8 of 80 (10%) developed SF allergy. Together these studies reported that 221 of 247 (89.5%) infants allergic to CMF could be effectively managed with SF. This overall performance approaches the clinical standard for hypoallergenic formula [95% confidence that 90% of allergic infants will not react (29)].

Frequency of allergy in a whole birth cohort. Arshad et al. (30) conducted an interesting study on the Isle of Wight, where a whole birth cohort of 981 infants (64% of total births agreed to participate during the 14-mo enrollment period) was followed to age 4 y. The study recorded histories of allergic disorders and assessed the correlation between these data and results of SPT to a variety of common allergens. Data were not adjusted for relative allergen exposure rates and, as mentioned earlier, SPT is known to overestimate the true incidence of food allergy. SPT results for the various allergens were as follows: house dust mite, 11.9%; grass, 7.9%; Alternaria, 4.8%; milk, 1.4%; and peanut, 1.2%. The lowest sensitization rate was for soy at 0.25%.

Food allergen reaction thresholds. Another method for ranking the potency of food allergens determines the minimum oral allergen dose required to initiate allergic symptoms. This dose will vary across a population of allergic patients, so the best comparator becomes the dose-response distribution within the allergic population. These data are difficult to obtain because patients with severe allergies must be challenged with increasing allergen doses until a positive reaction occurs. These types of experiments have been reported for only 5 food allergens (**Fig. 1**). The most important evidence concerns threshold doses for the most sensitive patients. No standards have been set for acceptable minimum allergen doses. However, for comparative purposes, we can apply the "safe for 90% of allergic patients" rule (the hypoallergenic infant formula standard) to the data in Figure 1 to estimate the following "safe" protein doses: peanut, 0.1 mg; hazelnut, 1 mg; egg and milk, ~3 mg; and soy, ~400 mg. Although the number of patients in these studies is relatively low, the >100-fold difference between the safe protein dose for soy and other allergens is striking. If confirmed, this difference should be considered when setting standards and selecting analytical methods appropriate for measuring soy allergens in food products and food production environments. A partial confirmation of this approach is found in a recent statistical analysis of published data by Blindslev-Jensen et al. (34). This report presented estimates of allergen doses causing reactions at rates of 1 per 1,000,000 and 1 per 100 of population. These data, summarized in **Table 1**, seem to be consistent with the 90% reactivity threshold numbers predicted for soy protein (1 in 10 at 400 mg protein vs. 1 in 100 at 40 mg protein).

TABLE 1

Reaction threshold levels of allergenic foods[1]

Food	One per million population		One per hundred population	
	Lower confidence limit	Predicted	Lower confidence limit	Predicted
	μg protein		*mg protein*	
Cow milk	0.072	0.576	0.279	0.886
Egg	0.003	0.10	0.023	0.152
Peanut	0.50	5.0	0.19	0.663
Soy	304	2440	12.92	40.71

[1] Modified from Bindslev-Jensen et al. (34).

Allergenic reaction severity. In addition to specific allergen frequency, Sicherer et al. (25) reported the severity of allergic reactions that occurred during the positive DBPCFC challenges (**Fig. 2**). In 13 y of experience with DBPCFCs, these investigators did not observe any severe allergic reactions to soy challenge.

In summary, SFs have been widely studied for the management of food allergy, mainly in infants and young children. In a variety of clinical study designs, soy protein has consistently been shown to be significantly less reactive than cow's milk protein (an observation without explanation at this point).

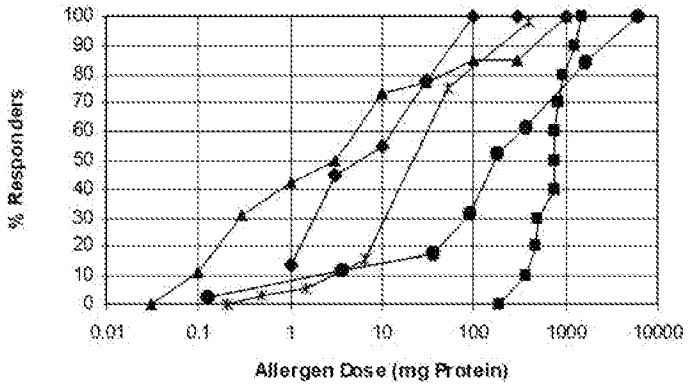

FIGURE 1 Food allergen reaction thresholds. Ingested allergen dose (mg protein) vs. % allergic responses in challenged patients. Allergens: ▲ peanut (31), ◆ hazelnut (32), ✕ egg (33), ● milk (27), ■ soy (27).

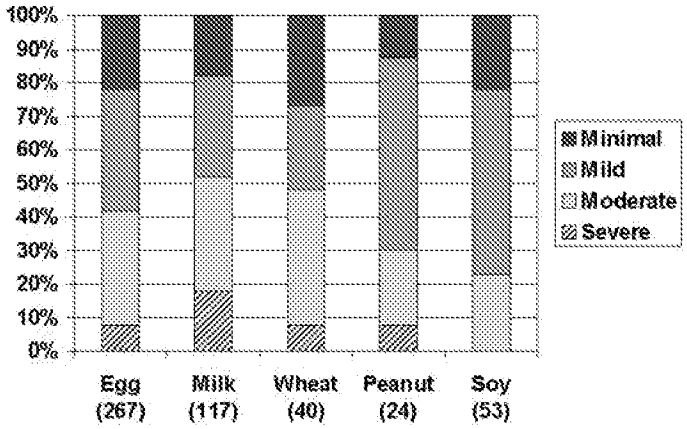

FIGURE 2 Allergic reaction severity. Percentage of challenge-positive patients vs. severity of elicited allergic reaction (number of food challenges). Adapted from Sicherer et al. (25).

Although extremely rare, severe soy allergies, including fatal reactions, have been reported.

Animal data

The basis for diminished immunological reactivity for soy protein in humans is unexplained. Is this a general property of soy or is low soy reactivity species specific? Data from 2 animal models of food allergy have been used to address these questions.

Oral sensitization model. The model using oral sensitization of guinea pigs, best described by Devey et al. (35), involves feeding an experimental protein for 33 d and then administering a rapid systemic antigen challenge on day 35. If sensitization has occurred, IgE and IgG1 antibodies will be produced. Both antibody classes will trigger anaphylactic reactions if activated by the presence of a cross-linking antigen. Antigen is injected and the animals are observed for anaphylactic symptoms, scoring for severity on a 0–5 scale (0 = no symptoms, 5 = death). The advantage of this model is that sensitization simulates antigen digestion and intestinal uptake. Disadvantages are that the model is not very sensitive, it does not include an oral challenge, and the anaphylactic response is usually dominated by an IgG1 response rather than an IgE response.

Results of feeding and challenge trials with CMF and SF are shown in **Table 2**. Two intact cow's milk-based formulas (Similac and Enfamil) stimulated strong immune responses that caused fatal anaphylactic reactions in all animals fed these products. A formula based on partially hydrolyzed cow's milk whey protein (Good Start) stimulated weaker but still significant reactions. Animals fed a hypoallergenic formula based on extensively hydrolyzed cow's milk casein (Alimentum) did not become sensitized as indicated by the absence of allergic symptoms. Interestingly, animals challenged after being fed a formula based on intact soy proteins demonstrated the lowest measurable symptoms of allergy, indicating very low relative reactivity. The significance of this result was confirmed with an important positive control: Guinea pigs were immunized by injection with soy formula mixed with an alum adjuvant on day 0 and challenged as before on day 35. These animals responded with severe allergic symptoms (4 deaths and 1 near death per 5 challenges), indicating that the lack of response to oral soy sensitization was not due to the inability of guinea pigs to produce antibodies to soy.

TABLE 2

Guinea pig oral sensitization: cow milk vs. soy formulas[1]

Product/protein	Anaphylaxis score[2]	Statistical group[3]
Similac/cow milk	5.00	A
Enfamil/cow milk	5.00	A
Good Start/partially hydrolyzed cow milk	3.11	B
Isomil/soy	1.00	C
Alimentum/extensively hydrolyzed cow milk	0.07	D
Isomil/soy—hyperimmunized[4]	4.80	A

[1] Adapted from Cordle, C. T., Duska-McEwen, G. & Janas, L., Ross Products, unpublished, 1995.
[2] Anaphylaxis score scale from no reaction = 0 to death = 5.
[3] Products with the same letter are not different (*t*-test, $P = 0.05$).
[4] Hyperimmunized using alum instead of oral sensitization.

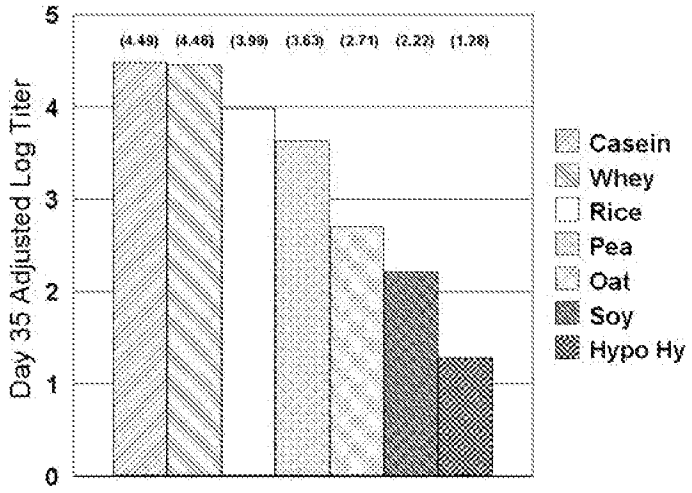

FIGURE 3 Immunogenicity of food protein systems using hyperimmunized rabbit model. Day 35 adjusted log titers ( ) = Log (day 35 IgG antibody titer/d 0 IgG antibody titer). Titer = reciprocal of antiserum dilution yielding an ELISA absorbance value of 0.3 after 10 min of substrate incubation. Hypo HY = data for a hypoallergenic casein hydrolysate. Data from Cordle et al. (39).

Hyperimmunization model. Rabbit hyperimmunization is a sensitive model for assessing immunological reactivity (36). This model uses relatively high doses of immunogen formulated with complete Freund's adjuvant and an aggressive immunization protocol with measurement of antibody responses using quantitative ELISA methods. The model has been used successfully to predict clinical performance of hypoallergenic formulas based on protein hydrolysates (37,38). **Figure 3** shows a comparison of the immunogenicity of various protein systems plus a clinically hypoallergenic casein hydrolysate as a low-end calibrator. Of the 6 intact protein systems tested at equal immunizing doses, soy was the least immunologically reactive (186-fold less reactive than cow's milk casein). This difference in ingredient reactivity is mirrored in infant formulas based on these proteins. **Figure 4** shows the relative immunogenicity of 3 CMFs compared with 4 SFs. The low-end calibrators in this figure are 2 hypoallergenic formulas based on extensively hydrolyzed casein (Alimentum and Nutramigen) and an essentially nonimmunogenic amino acid formula (EleCare). As a group, the SFs are 100 times less immunogenic than the CMFs. These data are surprising because all products contain intact proteins with similar molecular weight profiles.

Taken together, the animal data support the clinical findings of relatively low immunological reactivity for soy.

Biochemistry and immunochemistry of soy allergens

Food allergens are always complex mixtures of many potentially immunoreactive proteins. Within a food allergen system, individual allergens will also be affected differently by various processing methods. Therefore, the identity and the processing history of food proteins will determine their allergenic potentials and both must be considered in assessing allergen specificity and potency. Individual protein allergens are also complex, with several to many antibody recognition sites (epitopes) per protein. Epitopes can be either sequential (a particular linear amino acid sequence) or conformational (a group of nonlinear amino acids that are in proximity because of protein folding or assembly) and, for glycoproteins, may

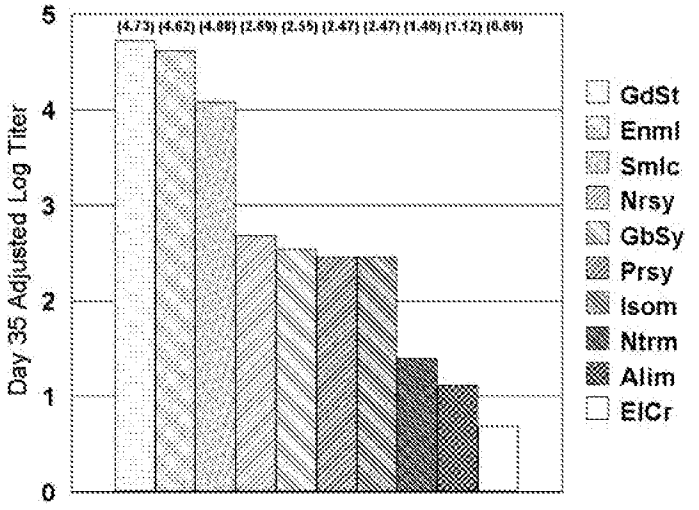

FIGURE 4 Immunogenicity of infant formula based on various food protein systems using the hyperimmunized rabbit model. Day 35 adjusted log titers ( ) = Log (day 35 IgG antibody titer / day 0 IgG antibody titer). Titer = reciprocal of antiserum dilution yielding an ELISA absorbance value of 0.3 after 10 min of substrate incubation. GdSt = partially hydrolyzed whey-based Good Start (Nestle), Enml = intact CM-based Enfamil (Mead Johnson), Smlc = intact CM-based Similac (Ross/Abbott), Nrsoy = intact soy-based Nursoy (Wyeth-Ayerst), GbSy = intact soy-based Gerber Soy (Mead Johnson), Prsy = intact soy-based Prosobee (Mead Johnson), Isom = intact soy-based Isomil (Ross/Abbott), Ntrm = hypoallergenic extensively hydrolyzed casein-based Nutramigen (Mead Johnson), Alim = hypoallergenic extensively hydrolyzed casein-based Alimentum (Ross/Abbott), ElCr = nonallergenic amino acid-based EleCare (Ross/Abbott). Data from Cordle et al. (unpublished, 1995) and Duska-McEwen et al. (45).

contain or be influenced by sugar moieties. This extensive complexity makes study results, immunochemical reagents, and control samples difficult to standardize and compare.

Understanding the working definitions of immunological terms used to describe FA and how these definitions relate to the analytical tools used to study FA helps promote experimental consistency and applicability. The first sentence of this article defined food allergy in terms of a clinical reaction to food. However, it is unsafe, unethical, and impractical to perform extensive basic and controlled research by challenging food-allergic patients. Model and surrogate experimental systems have been developed to address this problem. It is important to understand the strengths and weaknesses of these approaches. This is facilitated by a clear definition of terms. Unfortunately, definitions vary throughout the literature. For this article, the following represent simple, immunochemically logical descriptions: *antigenicity* is the ability of molecules (antigens) to interact with immunologically specific antibodies; *immunogenicity* is the ability of molecules (immunogens) to initiate antibody or cellular immune responses; and *allergenicity* is the ability of molecules (allergens) to initiate clinical allergic responses through IgE-mediated mechanisms.

Note that for this discussion, allergenicity is restricted to clinical indications of immediate-type hypersensitivity involving IgE. This is not a comprehensive definition, but is appropriate here because IgE-mediated type I reactions are the critical life-threatening clinical components of FA and because technologies effective in controlling type I allergy are likely effective with other forms of FA. An interesting debate concerns whether the presence of IgE antibody to a particular antigen is an indicator that the antigen is a type I allergen. The absence of an IgE response is strong evidence that the antigen is not a type I allergen but the presence of IgE antibody does not establish the capacity of the antigen to trigger allergic symptoms. A number of investigators have reported lack of correlation between in vitro (ELISA, RAST, and immunoblotting) and in vivo (SPT) measures of IgE reactivity and cross-reactivity, and clinical reactions detected using DBPCFC (40–43). Allergenic potency and specificity are most often measured using ELISA, RAST, or immunoblotting. However, without strong correlation with DBPCFC, these data must be considered only as indicators of allergenic potential and not proof of allergenic potency. This is particularly difficult for soy, where separation and purification of individual soy proteins is a significant challenge and where the number of soy-allergic patients to support DBPCFC research to identify individual allergens is very small. At this point, despite their known flaws, allergen potency measurements by ELISA and RAST and allergen specificity analysis by immunoblotting are the only analytical methods widely used.

At least 16 IgE-binding soy proteins with molecular masses from 7.5 to 97 kD may be involved in clinical allergy (44). Some of the major soy allergens are shown in **Table 3**. Key goals of research aimed at controlling soy allergy are to identify soy protein allergens, rank soy protein allergenic potency, and assess methods to decrease soy allergenic reactivity.

Immunoblotting is an important tool for identifying potential soy allergens. In this procedure proteins are separated by gel electrophoresis, usually under denaturing conditions (SDS-PAGE). The separated proteins are electrophoretically transferred onto an inert support where they are incubated with IgE obtained from known soy-allergic patients. After a washing step to remove unbound IgE, the blots are developed with an anti-IgE reagent that is radiolabeled or enzyme conjugated. The appropriate detection chemistry is then used to visualize those soy protein bands that bound IgE. A number of immunoblotting studies of soy allergens have been reported. A key immunoblot result from Awazuhara et al. (8) is shown in **Figure 5**. This study evaluated serums from 30 patients, the largest number of soy-allergic patients tested with common extracts and immunochemical reagents. Several important conclusions can be drawn from these data: Specific protein reactivity is highly variable between individual patients, making standardization of a common IgE anti-soy antisera pool extremely difficult. Some soy-allergic patients seem to react very weakly to only 1 or 2 soy proteins whereas others do not react to any. (Could these patients be sensitive to conformational epitopes not measured by the immunoblots?) Several protein bands are often positive but none is dominant, indicating that no single soy "super allergen" is detectable by this method.

TABLE 3

Major soy allergens

Allergen	Designation	Molecular mass (kD)	Comments
Soy hydrophobic protein	Gly m 1.0101	7.5	
Soy hull protein	Gly m 2	8	Aeroallergen
Soy profilin	Gly m 3	14	
Soy vacuolar protein	Gly m Bd 30 k	~34	
Glycinin		320–360	6 subunits
β-Conglycinin		140–180	3 subunits
Kunitz trypsin inhibitor		20	

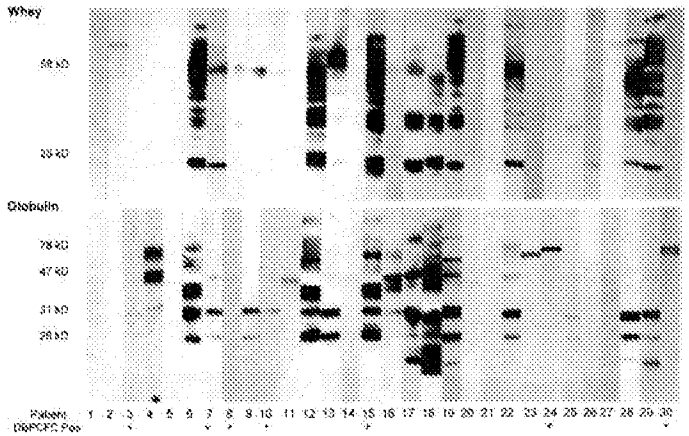

FIGURE 5 IgE-Soy protein reactivity patterns of 30 soy-allergic patients revealed by immunoblotting. Soy allergy confirmed by convincing recent history or by DBPCFC (7 patients). Reprinted with permission (Blackwell Publishing, Oxford) from Awazuhara et al. (8).

Weaknesses in immunoblot data must be remembered: individual studies contain relatively few patients and different patients give different results. Protein separation is accomplished under denaturing conditions that prevent detection of IgE binding to conformational epitopes that may play a significant or even dominant role. The presence and/or intensity of bands do not correlate with clinical reactivity. Cross-reactivity studies show many false-positive reactions. On the positive side, it is likely that immunoblot and ELISA data overestimate the number of clinically significant allergens. Elimination of a few high-affinity triggers of clinical allergy may substantially lower the overall allergenicity of soy.

Conclusions and future directions

A substantial and consistent body of human clinical and animal model data indicates that soy proteins tend to be less immunologically reactive than many other food proteins. The biochemical and immunological basis for these differences is currently unknown. Improved biochemical methods and immunochemical reagents will be required to better characterize and understand soy protein's unique immunological properties. In vitro methods that correlate better with DBPCFCs are needed, and these methods should be quantitative. Techniques must also allow for detection of conformational allergen epitopes. Finally, DBPCFC-positive patient antisera sample numbers available for study must be increased substantially and standardized antisera pools must be assembled and characterized.

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